Long-Term Follow-Up of 120 Patients with AIDS-Related Kaposi's Sarcoma Treated with Interferon Alpha-2A

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One hundred and twenty patients suffering from an AIDS-related Kaposi's sarcoma treated by 18 million units of recombinant alpha-2A-interferon daily were followed prospectively for a period of between one and six years. An overall complete response was observed in 35% of these patients; the figure was significantly higher in those who did not have a visceral localization or opportunistic infections. Total lymphocyte count, CD4 lymphocyte count, and CD4/CD8 ratio were significantly higher, and beta-2-microglobuline significantly lower, in the responders than in the non-responders. A multivariate analysis showed that localization of KS and CD4 count had independent predictive value, with an odds ratio of 35 for patients who had more than 300 CD4 cells at the onset of treatment versus those with less than 150. Patients whose initially negative p24 antigenemia remained negative during treatment had the highest frequency of complete response. Among patients with initially positive p24 antigenemia, those whose percentage decrease in antigenemia levels was greatest had a higher frequency of complete response. The cumulative probability of survival in responders was 62% at four years. These results demonstrate an anti-tumoral and anti-viral effect and prolonged survival in a group of patients whose initial immune parameters were relatively well preserved. However, these results do not permit us to conclude whether these well-responding patients were treated at the onset of illness, or whether their illness was naturally less evolutive. *J Invest Dermatol 95:161S–165S, 1990*

The etiology of Kaposi's sarcoma (KS), which has emerged as the most common AIDS-associated tumor, is probably multi-factorial [1]. Despite a multiplicity of existing descriptions, observations, and data, its natural history has not yet been well defined [2]. Although spontaneous regressions have been reported [3,4], they remain rare, and because it is now clear that KS has an impact on survival [5–7]—as well as on the quality of life—most authors agree that treatment is justified. Various kinds of treatment for KS have been initiated and evaluated, or are currently administered. These include diverse types of chemotherapy, interferon, zidovudine, radiotherapy, surgery, and intra-lesional and topical therapy [1,8–15].

The antiviral, immuno-modulatory, and anti-proliferative properties of interferon [16,17] led to the commencement of trials with the drug in 1981 [18,19]. However, the comparison of available data is complicated by the use of cohorts of different size and various preparations of interferons in a variety of schedules and dosage regimens [18–22]. In addition, follow-up on most of these trials has been short. Also, because different clinical staging systems exist, and because the immune deficit may be independent of clinical manifestations, the comparison of therapeutic effects and survival rates is difficult [23–26]. Data is not yet available on the long-term efficacy of treatment of KS with interferon.

We studied 120 patients with AIDS-related Kaposi's sarcoma treated with recombinant alpha-2a interferon (INF), over a period of six years, with a follow-up of at least one year after INF treatment was discontinued. Response and survival rates were correlated with the absence of opportunistic infections and visceral KS, and the preservation of immune status, as manifested by a high absolute number of CD4 lymphocytes.

Patients and Methods All patients who had AIDS (as defined by the Center for Disease Control criteria) and biopsy-proved KS, from March 1983 to November 1987, were entered in this non-randomized trial. Informed consent was obtained. Interferon treatment was not initiated alongside a concurrent acute infection or life-threatening complication in any patient. Pre-treatment evaluation included routine blood chemical testing and hematologic examination, chest radiography, cerebral scan, blood and urine culture for CMV, upper and lower gastrointestinal endoscopy, skin lesion photography, IgG, IgA, IgM and serum Beta-2 microglobulin dosage, and T-cell subsets count. P24 antigen was estimated in frozen sera before and during treatment, measured blind by the Abbott commercial assay, with concentrations calculated by linear regression and expressed in pg/ml.

One hundred and twenty male homosexuals, within an age range of 26–64 years (mean, 38), were entered in the study. Seven had been transfused, and three were IV drug users. Of patients who had had prior therapy, one had received Thymuline, two had received Isoprinosine, one had had radiotherapy, and one had had chemo-

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Abbreviations:
KS: Kaposi's sarcoma
INF: alpha-2a interferon
CMV: cytomegalovirus
CI: confidence internal
m: mean

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therapy. None had previously received interferon. Twenty-two had a past history of opportunistic infections. In 65 patients (54%), KS was cutaneous and/or in lymph nodes; in 41 (34%), KS was also found in the oral cavity; and in 14 (12%), KS was both cutaneous and visceral (either gastro-intestinal or pulmonary). The mean interval between diagnosis and the onset of treatment was 8 weeks (range, 1–52). Mean duration of treatment was 174 days (range, 47–447).

Patients received recombinant alpha-2a interferon (Hoffman-LaRoche). The drug was administered in an intramuscular dose of 9 million units on day 1, followed by 18 million units per day. In the case of mucosal or visceral KS, 36 million units per day were administered. After entry of 16 patients in a regimen of 36 million units, a high toxicity rate was observed; consequently this arm of study was closed to further entry. Thereafter, all patients received 18 million units per day until a response was achieved (complete, partial, stabilization), and the drug was continued for at least two months after maximal response. Preliminary results showed that patients with a past history of opportunistic infections did not respond to INF; this group was therefore also excluded from treatment.

Complete tumor response was defined as the disappearance of all palpable lesions, and in the case of persistent disinfiltrated lesions the absence of spindle cells and cellular proliferation in biopsy specimens. Partial tumor response was defined as greater than 50% reduction of the number of lesions, with no new lesions. Minor response was defined as a reduction of less than 50%. Stabilization was defined as a reduction of less than 25% in the number of lesions and an eventual increase in their number by no more than 25%. Progression was defined as an increase in the number of lesions by more than 25%. Toxicity was graded I to IV according to the World Health Organization's criteria for grading toxicity. During the first month, patients were assessed every week for toxicity and clinical response, and every month subsequently. Grade III or IV toxic events led to the discontinuation of INF until the return to normal of laboratory values; INF was re-introduced at full or half dose. Statistical analysis was carried out on dichotomous variables using Fischer's exact test; all p values given are two sided. Mortality analysis was performed using the PiL Life Tables and Survival Functions of BMDP Statistical Software Inc., Los Angeles, CA. Survival was calculated from the onset of treatment. A multivariate analysis was computed by logistic regression.

Results Clinical response to treatment according to localization of KS is shown in Table I. Patients with a minor response, a stabilization or progressively worsening disease were pooled into a single category, insofar as both minor response and stabilization always, over time, led to worsening of KS. A total of 42 patients (35%) had a complete response; 10 (8%) a partial response; and 68 (57%) a progressive disease. The frequency of a complete response was significantly higher among patients with isolated cutaneous or lymph node KS (28 of 65, or 44%) than among those with additional visceral KS (three of 14, or 21%). The frequency of prior opportunistic infections was lower among patients with a complete response (four of 42 or 10%) than among those with progressive disease (17 of 68 or 25%). In addition, patients with a complete response had had minor opportunistic infections (oesophagal candidiasis, n = 3; cryptosporidiosis n = 1). The interval between diagnosis and treatment, the mean duration of treatment, and the number of cutaneous lesions did not differ significantly between patients with a complete response, a partial response, or progressive disease (data not shown). The frequency of deaths was significantly lower among patients who had a complete response (12%) than among those with progressive disease (79%).

Among the 52 patients who had a complete or partial response, 30 (52%) suffered a relapse after a mean period of 50 weeks [mean follow-up, 1060 days (1–6 years)]. Of those 30 patients with a relapse, 25 had a second course of INF therapy; seven had a complete response at this second course. For the 22 patients still in remission, mean time without relapse was 133 weeks (range, 4–234). The cumulative non-relapse rate for complete responders was 64% at one year, 48% at 18 months, and 40% at 2 years (Fig 1).

Table II shows the initial values of biologic and immunologic criteria for responders (complete and partial response) and non-responders. The absolute counts for total lymphocytes and CD4+ cells and the CD4/CD8 ratio, were significantly higher among complete responders than among non-responders, and the level of IgA and beta-2 microglobulin were significantly lower. None of the responders had a positive blood CMV culture. We observed no complete response in patients who had a CD4 count under 180/mm³. Likewise, patients who had a beta-2 microglobulin serum under 4 mg/l [33 out of 49 (67%)] had a significantly increased rate of complete response ($p < 0.05$) as compared to patients whose count was higher. In the group of complete responder the mean CD4 count before interferon treatment was higher than immediately after treatment [$552/mm^3 \pm 254$ versus $400/mm^3 \pm 208$ ($p < 0.01$)]. The mean CD4 count did not differ significantly between patients who relapsed and those who did not.

In a multivariate analysis taking into account the localization of KS (cutaneous, mucosal, or visceral) and the above-mentioned biologic markers, two variables—localization and initial CD4 count—show an independent predictive value for clinical response (Table III). [Odds ratios, 6.25 (CI: 1.35, 33.3) for visceral KS versus cutaneous and 35.5 (CI: 4.3, 293) for patients with an initial CD4 count above 300 versus those with less than 150.]

Table I. Clinical Response with Alpha-2a Interferon According to Initial Localization and Prior Opportunistic Infections

Response Localization	Complete Response	Partial Response	Minor Response Stabilization Progressive Disease	Total
Cutaneous n (%) + Lymph. node	28 (44)	6 (9)	31 (47)	65
Cutaneous n (%) + Mucosal + Lymph. node	11 (26)	4 (10)	26 (64)	41
Cutaneous n (%) + Visceral + Mucosal + Lymph. node	3 (21)	0	11 (79)	14
Total n (%)	42 (35)	10 (8)	68 (57)	12
Opportunistic infection prior treatment	4 (18)	1 (5)	17 (77)	22
Deceased	8 (12)	6 (9)	53 (79)	67

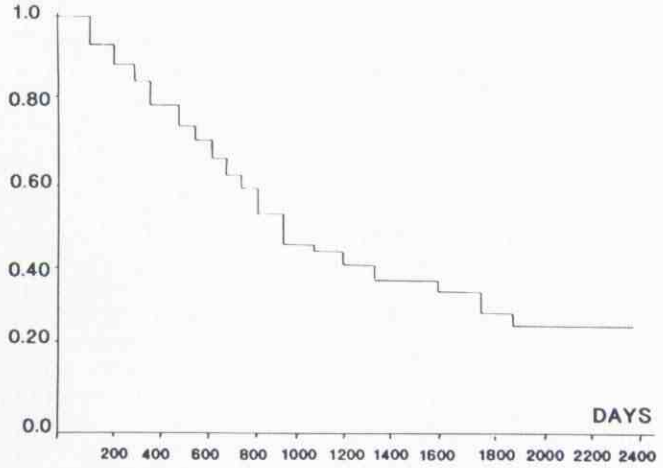

Figure 1. Cumulative non-relapse rate for patients who had had a complete response after interferon alpha-2a treatment. Time (days) after interruption of treatment. (Kaplan Meier curve.)

The P24 antigen value was analyzed for 76 patients. Fifty-two percent of patients with an initial negative value had a complete response, in contrast with only 29% of patients with a positive P24 antigen value ($p < 0.05$) (Table IV). Of the 49 patients whose initial P24 antigen value was positive, the drop in antigenemia during treatment was significantly larger in the group of complete responders (Table V), and seven of the nine patients who became antigen-negative had a complete response. Moreover, of the five antigen-negative patients who had evolutive lesions, four became antigen-positive during treatment.

As of June 1989, 68 patients had died, 36 were alive, and 16 were lost to follow-up. The crude case fatality rate was 57% and the cumulative probability of survival for all patients was 70% (CI, 78–62) at one year, 53% (CI, 62–47) at two years, 44% (CI, 54–35) at three years, 34% (CI, 45–23) at four years, and 23% (CI, 43–3) at five years. Median survival time for all patients from onset of treatment was 794 d (CI, 1017–571); for responders it was 1723 d (CI, 1949–1497) and for non-responders 375 d (CI, 467–839). Median survival time was 1137 d (CI, 694–256) for patients with cutaneous KS and 475 d (SE: 112) for patients with visceral KS. Table VI shows cumulative probability of survival for every subset of patients defined above.

Adverse effects included, firstly, a flu-like syndrome, which occurred in almost all patients, at least at the beginning of therapy. This syndrome was less frequent in patients receiving daily injections than when INF was administered every other day. Anemia, leukopenia, and trombocytopenia occurred to a minor degree, as well as elevated liver enzyme levels, which, however, never led to the interruption of treatment. Significant proteinuria occurred in seven patients, only one of whom was obliged to discontinue treatment. Of patients receiving 36 million units of INF a day, 75% (12 of 16) required a reduction in dosage, and 38% (six of 16) temporarily discontinued treatment due to adverse reactions. For those receiving 18 million units per day, treatment was reduced for 31% and temporarily discontinued for 18%.

Table III. Significant Odds Ratio in a Multivariate Analysis Taking into Account the Localization of KS and Biologic Markers of Table II

Variables	Odds Ratio	SE	p Value
Location of KS			
Visceral	1		<0.05
Mucosal	2.81	0.48	
Cutaneous	6.85	0.78	
Level of Initial CD4			
<150	1		<0.001
150 < CD4 < 300	6.4	1.1	
>300	35.5	1.07	

DISCUSSION

The initial rationale for the use of INF in AIDS-related KS was based on its immunomodulatory and anti-viral effects and its anti-proliferative properties [16,17]. Although spontaneous remissions in AIDS-related KS have been described [3,27], the antitumoral properties of INF are attested to by the results of our study, with an overall rate of significant remission of 43%. That figure is comparable to other studies using similar doses of INF [18–22,28], but the comparison is made difficult by the heterogeneity of the patients treated with respect to the extension of their KS, the existence of associated symptoms (particularly opportunistic infections), and their initial immune parameters. As in other studies, we observed an absence of significant remission in patients who, prior to or during treatment, developed opportunistic infections. However, we observed complete remissions in a small number of patients with oesophagal candidiasis (n = 3) or cryptosporidiasis (n = 1), but whose initial CD4 count was higher than 200/mm³. The absence of significant positive response in patients with cytomegalovirus-positive viremia suggests that this factor be considered equivalent to an opportunistic infection.

Although the various relevant studies have not all found localization of dissemination of KS to correlate with the degree of response to INF [19,29], we were able to demonstrate that the absence of any identified visceral localization, in particularly pulmonary localization, multiplies by a factor of six the probability of significant response.

As with most studies, we demonstrated a correlation between tumoral response and the initial number of lymphocytes, the CD4 count, the CD4/CD8 ratio, and $beta_2$ microglobulin level. However, our multivariate analysis showed that, of all biologic tests, only the initial CD4 count could be independently correlated with response, with a probability of response multiplied by a factor of 35 in patients with more than 300 CD4 cells as compared to those with under 150.

New classifications have been proposed for AIDS-related KS, taking into account the extent of lesions and the existence of associated symptoms [30,31]. Our data, together with those of others [18–24,32,33] suggest that the state of immune parameters, especially CD4 count [34], be introduced into any new classification. Groups of patients more homogenous with respect to these criteria would permit a more reliable comparison between the various studies.

Table II. Biologic Values Prior to Treatment of Responders (complete and partial response) Versus Non-Responders

Laboratory Parameters	Responders n = 52	Non-Responders n = 68	p Value
Total lymphocyte count m + SD (n/mm³)	1692 + 719	1250 + 495	<0.001
CD4 count (n/mm3) m + SD	485 + 228	291 + 206	<0.001
CD8 count (n/mm3) m + SD	728 + 483	581 + 282	NS
CD4/CD8 Ratio	0.8 + 0.44	0.54 + 0.37	<0.001
IgA (g/l) m + SD	3.69 + 1.73	4.35 + 2.17	NS
Beta 2 microglobuline m + SD (mg/l)	3.58 + 1.48	4.53 + 1.79	<0.01
CMV Viremia (number positive/number tested)	0/39	13/59	<0.01

Table IV. Clinical Response to Interferon Alpha-2a According to Initial HIV antigenemia (Ag)

	Complete Response	Partial Response	Stabilization	Progressive Disease	Total
P24 Ag Negative n (%)	14 (52)	5 (18)	3 (11)	5 (18)	27
P24 Ag Positive n (%)	14 (29)	7 (14)	7 (14)	21 (43)	49

The dose of 18 million units per day of INF was chosen as the maximum tolerable daily dose for a prolonged period. However, although controlled studies have demonstrated that doses under 6 million units per day give significantly poorer results than doses of 18 million units or more [18,20,29], the doses between 6 and 18 million units have never been tested. In our study, the response in the few patients who required dose reduction suggests that a dose of 9 million units per day could be effective, and justifies further investigation.

In the group of responders, the propensity to relapse is high (60% at two years), but certain patients (seven of 25) had a second complete response after renewed treatment. In our study we arbitrarily interrupted treatment with INF two months after maximum response. As long as there is no determining reason to believe that INF has more than an anti-tumoral action, and that it has any effect on the natural history of the disease, this attitude appears justified when a complete response is observed. In the case of partial response, a prolonged treatment can be instituted, so long as it is well tolerated and permits a stabilization of tumoral lesions.

Adverse effects are related to dosage and may necessitate a reduction in this dose. When the dose is administered daily, there are fewer, and more minor, side effects. They seem to diminish with time, only rarely interrupting the treatment and allowing more than half of patients to continue working. Side effects appear less frequent and less serious in patients for whom the treatment is effective.

Interestingly, as in other studies [18–20,22,28], we did not find improvement in immune functions as measured by the CD4 count, which was lower after treatment than before. Whether this decrease was caused by the INF, through the intermediatry of a leukopenia, or by the natural history of the disease, needs investigation. However, several months after interruption of treatment the CD4 count tends to return to its original level. It is possible that INF induces a prolonged stabilization in responders and even an increase in CD4 count [21], but this could only be demonstrated by a study comparing groups of patients with comparable immune parameters and undergoing treatment by other drugs, or with no treatment.

We have shown that a strong correlation exists between the strength of response and the presence of p24 antigen serum, as well as with its decrease when it is present. The anti-retroviral effect of INF has already been demonstrated in Murine leukemia virus, in inhibiting viral replication by preventing viral assembly and maturation [35]. Equivalent results have been obtained in vitro on the replication of HIV [36]. Our results do not indicate that the anti-tumoral action of INF is necessarily mediated by its anti-viral action; indeed, the intensity of response is very closely correlated with the intensity of the initial immune deficit, whereas the Murine model shows that the anti-tumoral effect requires still functioning T cells [37]. Moreover, zidovudine, which of all products in use in humans has the greatest anti-retroviral effect, appears to have no significant effect on Kaposi's sarcoma [13]. Other studies, on p24 antigen-positive subjects, have demonstrated a similar response to the use of INF, correlated with the intensity of immune deficit [21,22]. Although these results do not permit us to establish a physiopathologic explanation for the action of interferon, they do allow us to use the serum p24 antigen as a predictive element for patient response. Generally, the outlook is good if a patient's p24 antigenemia is negative and remains so (52% of complete response in our group), or if the level of p24 antigenemia decreases significantly. Whatever the explanation for the anti-viral effect, its existence is an additional rationale for the use of INF, alone or in association with other drugs, in patients with well-preserved immune parameters and a KS or other forms of HIV infection.

The survival rates of our group of homogenously treated patients are in the upper limit of results published elsewhere [5–8,20]. However, the comparison is flawed, because the stage and severity of immune deficit of the patients studied by these various groups are different. For example, as our study progressed, we pre-selected patients participating in the program, excluding those with prior opportunistic infections, therefore introducing a bias towards the best responders. A significant difference in survival rates was found for responders versus non-responders, as well as in patients who had isolated, cutaneous forms of KS versus those with visceral KS. This difference could be simply the reflection of a lesser incidence of opportunistic infections, an earlier stage of illness or a better spontaneous prognosis in responders. Various studies have shown that survival is dependent on clinical and biologic presentation. Previous opportunistic infections and symptoms such as fever, weight loss, and chronic diarrhea lower life expectancy, as do low levels of CD4 cells, CD4/CD8 ratio, and lymphocyte proliferative response to PHA, a high level of IgA [23,24], delayed skin tests, a high level of labile acid interferon [26] or a low proliferative response to *Escherichia Coli* [2]. Initial localization of KS also appears to influence prognosis; better survival rates are obtained with localization on the lower body [34].

Taylor's study [24] demonstrated that it is above all the initial immunologic presentation that conditions survival, independently of the type of treatment; long-term survival without therapy has already been described [4] and in Taylor's study 25% of patients received no treatment whereas 50% were on INF. Thus the difference in survival rates appears to be attributable to a better spontaneous prognosis for KS with well-preserved immune parameters. The most evident benefit of INF resides in its anti-tumoral effect. It is thus possible that INF could act on that fraction of deaths imputable to tumoral proliferation.

Our study has demonstrated a positive anti-tumoral effect of INF in KS, but a real evaluation of its benefits demands, first, a redesign of the classification of AIDS-related KS, taking into account the immunologic parameters that are the preponderant factor in prognosis [34]; this should serve as a basis for long-term control-based studies. However, the evident effect of interferon on HIV proliferation in vivo makes it clear that INF has a place in the therapeutic arsenal against HIV infection.

Table V. Evolution of p24 HIV Antigenemia (Ag) During Treatment by Interferon Alpha-2a

	Number of Patients	Initial 24 Ag m (pg/ml)	P24 Ag Level During Treatment m (pg/ml)	% Decrease	p Value
Complete response	14	212	39	81%	<0.01
Partial response	7	1339	409	69%	<0.01
Stabilization and progressive disease	28	501	342	32%	<0.01
Total	49	539	265	51%	

Table VI. Cumulative Probability of Survival According to Initial Localization of Kaposi's Sarcoma and Interferon Alpha-2a Respons

	Cutaneous Kaposi's Sarcoma	Visceral Kaposi's Sarcoma	Responders	Non-Responders
Total	65	55	52	68
Dead	33	35	15	53
Censored	32	20	37	15
Cumulative Probability of survival at 1 year	92%	57%	94%	51%
2 years	75%	39%	90%	22%
3 years	52%	34%	78%	16%
4 years			62%	

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